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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/524,198	02/10/2005	Petrus Johannes Maria Nuijten	I-2002.013 US	3848

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INTERVET INC.
PATENT DEPARTMENT
PO BOX 318
MILLSBORO, DE 19966-0318

EXAMINER	
SHAHNAN SHAH, KHATOL S	

ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/524,198	NUIJTEN ET AL.	
	Examiner	Art Unit	
	KHATOL S. SHAHNAN SHAH	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *2/07/2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/10/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

RESPONSE TO AMENDMENT

1. The amendments filed 2/07/2008 have been entered into the record. Claims 1-6 and 11-20 have been cancelled. Specification multiple pages have been amended. Claims 7-10 have been amended. Claims 7-10 are pending and under examination.

Objections Withdrawn

2. Objection to drawing made, in paragraph 3 of the office action mailed 10/03/2007 is withdrawn in view of applicant's submitting of replaced figures.

3. Objection to the specification made in paragraph 7 of the office action mailed 10/03/2007 is withdrawn in view of applicant's amendments of 2/07/2008.

4. Objection to claim 10 made in paragraph 9, of the office action mailed 10/03/2007 is withdrawn in view of applicant's amendments of 2/07/2008.

Objections Maintained

5. Objection to the specification in regard to sequence compliance made in paragraph 5 of the office action mailed 10/03/2007 is maintained. Applicant has amended the specification to include sequence identifiers submitted, however, the CRF submitted with the replacement sequence listing is flawed technically and not entered into the database.

Rejections Withdrawn

6. Rejection of claims 7-9 under 35 U.S.C. 101 made in paragraph 11 of the office action mailed 10/03/2007 is withdrawn in view of applicant's amendments of 2/07/2008.

Rejections Maintained

7. Rejection of claims 7-9 under 35 U.S.C. 112 first paragraph made in paragraph 13 of the office action mailed 10/03/2007 is maintained.

The rejection was as stated below:

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 7- 9 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claims 7 - 9 recite a group of immunogenic protein and fragments thereof. With respect to % identity or numbers of substitutions/deletions/additions where said immunogenic fragment has a sequence homology of at least 93%, 94%, preferably 95% and more preferably 96% to SEQ ID NO: 2. The specification recites "Again another embodiment of the present invention relates to the use of a 22.5 kD *Streptococcus uberis* protein, or an immunogenic fragment of that protein having a length of at least 6 amino acids, wherein that protein or immunogenic fragment thereof has an amino acid sequence homology of at least 70%, preferably 80%, more preferably 85% with the amino acid sequence as depicted in SEQ ID NO: 2 for the manufacturing of a vaccine for combating *Streptococcus uberis* infection. Even more preferred is a sequence homology of 90%, 95%, 97%, 98%, 99% or even 100% in that order of preference (see page 9)." The specification and the claims do not indicate what distinguishing attribute are shared by the members of the genus. Thus the scope of the claims include numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. Since the disclosure fails to describe the common attributes or characteristics that identify the members of the genus, and because the genus is highly variant, just naming the proteins is insufficient to describe the genus and derivatives thereof. Thus applicant has not described a function, which is shared by the full length or derivative thereof, which would adequately describe the genus. One skilled in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Since the specification gives no guidance on or exemplification of how to anticipate the specific homologues, analogues or derivatives thereof, having variant amino acid sequences from claimed proteins. Substitution of amino acids into a

known sequence as well as identifying and using fragments of proteins containing an isolated functional domain of a protein is within the realm of protein chemistry and is one of the most unpredictable areas of protein chemistry. For example Burgess et al. (J of Cell Biology, 1990 Vol. 111, pp.2129-2138) teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. Furthermore, Lazar et al (Molecular and Cellular Biology, 1988, Vol. 8, pp. 1247-1252) teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein. Streptococcus uberis genome DNA and its proteins are known in the art for example see Jayarao et al and Leigh et al. (Prior art of recode) However, these references are silent about variant amino acid sequences from these claimed proteins.

The Guidelines for the Examination of Patent Application Under 35 U.S.C. 112, 1st paragraph "Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice or by disclosure of relevant, identifying characteristics, i.e. structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in the position of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 3rd column).

Since the disclosure fails to describe the common attributes or characteristics that identify the members of the genus, and because the genus is highly variant, SEQ ID NO: 2 is insufficient to describe the genus of % homology variants or fragments

thereof. Adequate written description requires more than a mere statement that is part of the invention and a reference to a potential method of isolating it. The protein itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. LTS*. 18 USPQ 2d 1016. Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Application Under 35 U.S.C. 112, 1 "Written Description" Requirement, Federal Register, Vol. 64, No.244, pages 71427-71440, Tuesday December 21, 1999.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP 2163.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In Regents of the University of California v. Eli Lilly & Co., the court stated:

"A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name of the claimed subject matter sufficient to distinguish it from other materials. Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606; In re Smythe, 480 F.2d 1376, 1383, 178 USPQ 279, 284-85 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain, species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus...."). Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the

sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. The MPEP does state that for generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP 2163. Although the MPEP does not define what constitute a sufficient number of representative, the Courts have indicated what do not constitute a representative number species to adequately describe a broad generic. In Gostelli, the Court determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. In re Gostelli, 872 F.2d at 1012, 10 USPQ2d at 1618.

Applicant's arguments of 2/07/2008 have been fully considered but they are not persuasive.

Applicant argues that:

- Claim 7 is now amended to add that the claimed protein is immunoreactive with antisera from *Streptococcus uberis* infected cows in addition to having the required sequence homology. This characteristic is illustrated in Example 2, beginning on page 21, and in the immunoblot gels illustrated in Figure 2. Following the procedures of Example 2, the ordinary skilled practitioner can without undue experimentation determine whether or not a particular protein of at least 93% (claim 7) or at least 96% (claim 8) homology meets the functional requirement set forth in the claims.

In response to applicant's arguments it should be mentioned that in an predictable art adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus. Page 21 and figure 2 only describe the 22.5 kD isolated protein and because the genus is highly variant, SEQ ID NO: 2 is insufficient to describe the genus of % homology variants or fragments thereof. The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the

sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163.

8. Rejection of claims 7-9 under 35 U.S.C. 102 (b) made in paragraph 15 of the office action mailed 10/03/2007 is maintained.

The rejection was as stated below:

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 7 - 9 are rejected under 35 U.S.C. 102(b) as being anticipated by Leigh et al. (vaccine, vol. 17, pp. 851-857, 1999).

The claims are drawn to a 22.5 kD *Streptococcus uberis* immunogenic protein. Leigh et al. teach *Streptococcus uberis* immunogenic proteins as vaccine antigens ranging from 20 kD to 66 kD (see page 854, figure 1). Leigh et al. do not explicitly teach fragments which has a sequence having at least 93%, 94%, preferably 95% and more preferably 96% homology to SEQ ID 2. These fragments will be inherent in the proteins taught by Leigh et al.

Applicant's arguments of 2/07/2008 have been fully considered but they are not persuasive.

Applicant argues that:

- The rejection over Leigh *et al.* is respectfully traversed. This reference teaches the preparation of antigen by incubating *Streptococcus uberis* in BHI BROTH and removing bacteria by centrifugation. The supernatant from centrifugation is clarified by filtration, from which proteins are precipitated. There proteins from the original supernatant are purified and used to make a vaccine. (See page 852, column 2, sections 2.2, 2.3 and 2.4). A gel of antigen proteins is presented in Figure 1 on page 854. In the present application the claimed protein is a 22.5 kD cell wall associated protein that would not be found in the supernatant from which Leigh *et al.* purified their antigen. On page 21, Example 2, beginning line 15, it is

stated that "S. uberis was grown under standard conditions and then treated with mutanolysin, an enzyme that degrades the cell wall of Streptococcal species. In this way, cell wall associated proteins will be released. After centrifugation these released proteins will be present in the supernatant. Both, supernatant and cell pellet were run on the protein gel." Beginning line 25, it is stated "[i]n the lane comprising the purified 22.5 kDa expression product a clear band of approximately 23 kDa was visible. In Western immunoblotting this band reacted positive (sic) with antibodies from *S. uberis* infected cows (see Fig. 2 lane 6). In addition a band with a similar molecular weight was observed in lanes 3 and 5 which contained supernatant of mutanolysin treated S. uberis cells. Slight differences in molecular weight are caused by the extra HIS residues of the E. coli expression product. This indicates that the 22.5 kDa protein is located in the cell wall or on the surface of *S.uberis* cells." In the absence of an enzyme that degrades a cell wall, which is not reportedly used by Leigh *et al.*, the antigens in the supernatant purified by Leigh *et al.* could not be cell wall associated proteins as in the present invention.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., isolated protein from cell wall using an enzyme i.e. mutanolysin) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

As the applicant recites above the reference teaches the preparation of antigen by incubating *Streptococcus uberis* in BHI BROTH and removing bacteria by centrifugation. The supernatant from centrifugation is clarified by filtration, from which proteins are precipitated. There proteins from the original supernatant are purified and

used to make a vaccine. (See page 852, column 2, sections 2.2, 2.3 and 2.4). It is possible that the above supernatant also contain the proteins which are located in the cell wall or on the surface of *S.uberis* cells and released by centrifugation.

New Rejections

9. Amended claims 10 is also rejected under 35 U.S.C. 112 first paragraph. Claim 10 recite a group of immunogenic protein and fragments thereof, for the rejection see paragraph 7 above.

10. Amended claims 10 is also rejected under 35 U.S.C. 102 (b) as being anticipated by Leigh et al. (vaccine, vol. 17, pp. 851-857, 1999).

Claim 10 recite a group of immunogenic protein and fragments thereof, for the rejection see paragraph 8 above.

Conclusion

11. No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Khatol Shahnan-Shah whose telephone number is 571-272-0863. The examiner can normally be reached on Mondays and Wednesdays from12:30 PM-6:30 PM and Thursdays from12:30 PM-4:30 PM If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Khatol Shahnan-Shah . B.S.,
Pharm, M.S.
Biotechnology Patent Examiner
Art Unit 1645

/Shanon A. Foley/
Supervisory Patent Examiner, Art Unit 1645